[redacted]

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,073	04/09/2001	Ke-Wen Dong	#651	7413

24395 7590 12/02/2003

HALE & DORR LLP
THE WILLARD OFFICE BUILDING
1455 PENNSYLVANIA AVE, NW
WASHINGTON, DC 20004

EXAMINER	
COOK, LISA V	
ART UNIT	**PAPER NUMBER**
1641	18

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/829,073	DONG ET AL.	
	Examin r	Art Unit	
	Lisa V. Cook	1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *20 October 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: of the reasons set forth in the previous office Action

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *1-9 and 19*.

   Claim(s) withdrawn from consideration: *10-18,20 and 21*.

8. ☒ The drawing correction filed on *20 October 2003* is a)☒ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *17*.

10. ☐ Other: _____

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
11/26/03

[redacted]

Continuation She t (PTOL-303) **Application No.**
09/829,073

Continuation of 2. NOTE: The claims have been modified to recite the utility of a glycosylated recombinant human ZP3 expressed in human ovarian cells. The previous claims did not require the glycosylation of recombinant human ZP3 nor did they require the production of said ZP3 from a human ovarian cell. The new claim limitations require additonal search and consideration of the prior art. Accordingly the amendment will not be entered.

Alisa Wood
11/17/03

ADVISORY ACTION

Election/Restriction

1. Applicant's response to the Final Office Action mailed 20 May 2003 (Paper #16 filed 10/20/03) is acknowledged. The amendment filed therein has not been entered. Currently, Claims 1-9, and 19 are under consideration.

OBJECTIONS WITHDRAWN

Drawings

2. The drawings in this application are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948).

Applicants corrected drawings filed 10/20/03 in paper #16 were stamped approved by the Draftsperson. The objection is withdrawn.

OBJECTIONS MAINTAINED

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form 1449 has cited the references they have not been considered.

4. The information Disclosure Statement filed 8/5/02 has been considered as to the merits before first action.

Applicant has filed an information disclosure statement in paper #17 filed 10/20/03 After Final . The IDS has not been considered because all the requirements of 37 CFR 1.97were not meet. Specifically a statement is required. The objection is maintained. Please see 37 CFR 1.97(d) and (e).

INFORMATION DISCLOSURE STATEMENT

(c) An information disclosure statement shall be considered by the Office if filed after the period specified in paragraph (b) of this section, provided that the information disclosure statement is filed before the mailing date of any of a final action under § 1.113, a notice of allowance under § 1.311, or an action that otherwise closes prosecution in the application, and it is accompanied by one of:

(1) The statement specified in paragraph (e) of this section; or

(2) The fee set forth in § 1.17(p).

(d) An information disclosure statement shall be considered by the Office if filed by the applicant after the period specified in paragraph (c) of this section, provided that the information disclosure statement is filed on or before payment of the issue fee and is accompanied by:

(1) The statement specified in paragraph (e) of this section; and

(2) The fee set forth in § 1.17(p).

(e) A statement under this section must state either:

(1) That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or

(2) That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.

(f) No extensions of time for filing an information disclosure statement are permitted under § 1.136. If a bona fide attempt is made to comply with § 1.98, but part of the required content is inadvertently omitted, additional time may be given to enable full compliance

OBJECTIONS MAINTAINED

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994).

Van Duin et al. disclosed the expression and purification of human zona pellucida protein ZP3 produced by Chinese hamster ovary. The recombinant human zona pellucida protein ZP3 induces the human sperm acrosome reaction and promotes sperm egg fusion. See abstract and page 608, 1st column, 2nd paragraph.

ZP3 is a zona pellucida protein 3 as supported by the disclosure on page 2 lines 5-6. The protein concentration of ZP3 was measured in an immunoassay employing coated plates/matrix. The binding of ZP3 to sperm was also taught and evaluated via the human sperm acrosome reaction assay on page 61 and the hamster egg penetration assay on page 611. With respect to the protein concentration of ZP3, the reference outlined several different optimal concentrations of ZP3. In the ZP3 quantitative determination on page 610 the human zona pellucida contained approximately 5ng ZP3. In the human sperm acrosome reaction assay the concentration of recZP3 was 15-20ng/μl or .015-.020ng/ml. In the hamster egg penetration assay the final concentration of recZP3 raged from 2 to 32ng/ml. Therein reading on the different concentrations recited in claims 2-8.

II. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Van Duin (WO 92/03548).

Van Duin disclosed a polypeptide and functional derivatives thereof, which have human ZP3 activity or human ZP3 antigenicity. The polypeptides can be produced either synthetically or by recombinant DNA technology. Specifically, the polypeptide to be expressed is coded for by a DNA sequence or more accurately a nucleic acid sequence. The nucleic acid sequence is optionally transcribed and translated to the target polypeptide via cloning into a vector transformed into a host cell. The vector may be self-replicating or it may integrate into the DNA of the host. (See page 2) Different host cells can lead to different polypeptides. (Prokaryotes are not adapted for glycosylation, Eukaryotes have the means of glycosylation, but yeast cells give a different glycosylation pattern than mammalian cells).

ZP3 binding to eggs and sperm are evaluated on page 11 and figure 7.

Response to Arguments

6. Applicant argues that the "recombinant human zona pellucida protein 3" (ZP3) in the references of Van Duin et al. is a protein not a glycoprotein. In response to this argument, it is noted the "glycoprotein" distinction is not recited in the instant claims. Further Van Duin teaches the ZP3 to be a glycoprotein; See page 607 1st paragraph last line in Biology of Reproduction.

In response to applicant's argument that the references of Van Duin et al. fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the expression and purification of ZP3 produced by human ovarian cells) are not recited in the rejected claim(s).

Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Van Duin (WO 92/03548) measures the inhibition of sperm-zona binding caused by ZP3 antibodies bound to the egg, while the instant invention measures binding of ZP3 to sperm. This argument was carefully considered but not found persuasive because Van Duin et al. teach ZP3 binding to sperm. See page 13 - figure 7. With respect to the binding activity being inhibition, it is noted that the claims do not make such a distinction. The claims merely require the measurement of sperm activity, which reads on binding inhibition.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 2-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Duin (WO 92/03548).

Please see previous discussions of Van Duin as set forth above.

Van Duin differ from the instant invention in not specifically identifying the concentration of human zona pellucida protein ZP3.

However, Van Duin discloses the claimed invention except for specific concentrations of ZP3. It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the concentration of reagents to the specific concentrations in claims 2-8 in a binding assay as a means of optimizing the assay, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

Response to Arguments

Applicant contends that the inventive glycosylated ZP3 expressed in human ovarian cells triggers an acrosome reaction within one hour at a concentration of below 1μg/ml while the biological activity of the Van Duin et al.'s ZP3 protein is at least 10 times lower than that of the present invention. This argument was carefully considered but not found persuasive because the limitations were not recited in the instant claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., glycosylated ZP3 expressed in human ovarian cells and their involvement in an acrosome reaction) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that Van Duin (WO 92/03548) measures the inhibition of sperm-zona binding caused by ZP3 antibodies bound to the egg, while the instant invention measures binding of ZP3 to sperm. This argument was carefully considered but not found persuasive because Van Duin et al. teach ZP3 binding to sperm. See page 13 - figure 7. With respect to the binding activity being inhibition, it is noted that the claims do not make such a distinction. The claims merely require the measurement of sperm activity, which reads on binding inhibition.

II. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Duin (WO 92/03548) in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187).

Please see Van Duin as set forth above.

Van Duin differs from the instant invention in not specifically teaching the detection assay in which one of the reagents is fixed to a matrix (i.e. micro titer plates).

However, Maggio disclose enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (micro titer plates). See page 186.

Van Duin and Maggio are analogous art because they are from the same field of endeavor, both inventions teach binding assay methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a matrix/micro titer plates as taught by Maggio in the assay method to detection ZP3/sperm binding of Van Duin because Maggio taught that micro plates or micro titer plates "are very convenient to wash thereby reducing labor in assay procedures". Page 186, last line.

III. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994) or Van Duin (WO 92/03548) in view of Foster et al. (U.S.Patent#4,444,879).

The teachings of Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994) or Van Duin (WO 92/03548) are set forth above. Both references teach binding buffers and/or washing buffers in their assay techniques. However, these references fail to teach the assay as a kit.

However, kits are well known embodiments for assay reagents. Foster et al. (U.S. Patent #4,444,879) describe one example. In their patent kits including the reactant reagents, a micro plate, positive controls, negative controls, standards, and instructions are taught. See figure 6, and column 15, lines 10-34.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to take the binding/detection assay as taught by Van Duin et al. (Biology of Reproduction, 51, 607-617, 1994) or Van Duin (WO 92/03548) and format them into a kit because Foster et al. teach that it is convenient to do so and one can enhance sensitivity of a method by providing reagents as a kit. Further, the reagents in a kit are available in pre-measured amounts, which eliminates the variability that can occur when performing the assay.

Response to Arguments

Applicant contends that the prior art references do not teach ZP3 produced from an ovarian cell with acrosome reaction activity as the instant invention. Accordingly, the prima facie obviousness is not possible because the combination do not cure this deficiency. However, these arguments have been addressed above.

Further, the instant claims do not clearly distinguish the ZP3 from/over the prior art compound. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therein the rejections are maintained.

8. For reasons aforementioned, no claims are allowed.

9. **THIS ACTION REMAINS FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Remarks

10. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Harris (U.S.Patent#5,837,497) teaches methods related to the purification and isolation of DNA sequences encoding the zona pellucida proteins from various mammalian species. The zona pellucida is a complex matrix surrounding the mammalian oocyte, formed of glycoproteins secreted by ovarian cells. Zone pellucida (ZP) glycoproteins perform a number of different functions. For example, the mouse ZP has been shown to provide structural integrity to the matrix, to be a sperm receptor in the matrix, to induce the sperm acrosome reaction on the surface of ZP, and to maintain binding between the sperm/egg as a secondary receptor. (Column 1, Lines 24-52)

In example 11, Harris et al. isolate and purify a human DNA sequences encoding human zona pellucida proteins ZPA and ZPB. These glycoprotein structures were found to be 92.6% homologous to the instant inventive products. (MPSRCH comparing protein-protein database search utilizing Smith-Waterman algorithm - A).

B. Ozgur et al. (Molecular Human Reproduction, Vol.4, No.4, pp.318-324, 1998) teach direct evidence of the binding process dependency upon the recognition of oligosacchardes sequences associated with zona pellucida glycoproteins.

C. Harris et al. (WO 94/11019) teach methods related to the purification and isolation of DNA sequences encoding the zona pellucida proteins from various mammalian species. The zona pellucida is a complex matrix surrounding the mammalian oocyte, formed of glycoproteins secreted by ovarian cells. Zone pellucida (ZP) glycoproteins perform a number of different functions. For example, the mouse ZP has been shown to provide structural integrity to the matrix, to be a sperm receptor in the matrix, to induce the sperm acrosome reaction on the surface of ZP, and to maintain binding between the sperm/egg as a secondary receptor. (Page 1 and Page 2) In example 11, Harris et al. isolate and purify a human DNA sequences encoding human zona pellucida proteins ZPA and ZPB. These glycoprotein structures were found to be 92.6% homologous to the instant inventive products. (MPSRCH comparing protein-protein database search utilizing Smith-Waterman algorithm - A).

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
(703) 305-0808
11/17/03